

**PETITION FOR RECONSIDERATION OF DENIAL OF SUITABILITY
PETITION SP 04P-0127/CP 1, ANTIROBE® (clindamycin hydrochloride)**

The undersigned submits this petition for reconsideration of the decision of the Commissioner of Food and Drugs in Docket No. SP 04P-0127/CP 1.

A. Decision Involved

On May 13, 2004, the Center for Veterinary Medicine denied suitability petition for Smart Drug Systems, Inc.'s ("Smart Drug") ANTIROBE® (clindamycin hydrochloride). The stated reason is that the change in the product's strength and dosage regimen from the pioneer's dosage strength and dosing regimen necessitates additional data to establish its safety and efficacy data in the drug's targeted animal - dogs.

B. Action Requested

Smart Drug is requesting the Commissioner to grant its suitability petition and reverse the Center for Veterinary Medicine's ("CVM") denial.

C. Statement of Grounds

Section 521(n)(3) of the Federal Food, Drug, and Cosmetic Act ("FFDCA") requires the agency to approve a suitability petition for a generic drug product that differs in strength from the pioneer unless the agency finds that additional investigations are necessary to determine the products safety and effectiveness.¹ The strength of the product by its very meaning would also include the dosing regimen. Indeed, there is nothing in the statute or the agency's regulations that require the dosing regimen to remain the same as long as the company can established, after the granting of the suitability petition, that a stronger once per day dosing regimen is bioequivalent to the pioneer's lesser strength twice a day dosing regimen. In this instance, Smart Drug has proposed to increase the strength of clindamycin hydrochloride from the pioneer's dosing of 2.5 mg/lb/twice a day to dosing 5.0 mg/lb/once per day. This change, however, does not raise any safety or efficacy issues as long as the product is bioequivalent to the pioneer drug.

In regards to the need for additional safety data, it is clear from pioneer's FOI summary for NADA 120-161 that all the pivotal safety studies conducted to establish the safety of

¹ While the agency does not specifically set out its basis for denial, there is no reason to believe it was related to changing the dosage form from capsules to tablets. In this regard, there is virtually no difference between the two dosage forms. Indeed, the Center and Center for Drug Evaluation and Research have routinely approved suitability petitions in which the dosage form was changed from capsule to tablet and vice versa. To the extent that there could be a difference in release due to the change in dosage form, this would be evident in the bioequivalence work that will need to be completed once the suitability petition is granted.

clindamycin hydrochloride were actually conducted with double the strength, once a day dosing rather than the twice a day dosing that was approved by the agency. As you know, it is typical of pathology studies to be conducted with a single dose regimen rather than a twice a day dose regimen.

More specifically, in both the "One-year Oral Toxicity Study in the Dog" and the "Chronic 1-year Oral Toxicity Study in the Dog" dosing was once a day, as we propose. The sponsor dosed the dogs, in both of these safety studies, at 13.6, 45.5 and 136.4 mg/lb/day. We are proposing a daily dose of 5.0 mg/lb/day. The doses given in the pioneer's studies reflect a 2.7X, 9.1X and 27.3X level of our proposed daily dose, with no adverse effects seen. The studies conducted by the pioneer sponsor clearly support our proposed tablet strength as safe in the dog without any further evaluation. As you know, the agency is required to rely on the pioneer safety studies when the pioneer safety studies clearly support the safety of the generic animal drug. Accordingly, we believe that there is sufficient safety information to support the use of clindamycin hydrochloride at a once a day dose of 5.0 mg/lb/day.

The efficacy of our generic clindamycin hydrochloride in dogs, similarly, does not need to be evaluated for our requested increase in strength of our tablet. Antibiotics are different from many other drugs as they do not have a direct effect on the physiology and biology of the host but work by directly killing or inhibiting the growth of bacteria invading the host. Indeed, the most important factor in antibiotic therapy is to maintain blood levels above the minimum inhibitory concentration (MIC) for a specific pathogen. Basic pharmacokinetics leads one to expect an initial peak in the serum level of an absorbed drug, followed by a depletion (elimination or excretion) curve. A lower dose would have a depletion curve that would go below the MIC levels sooner than a higher dose of the same drug. This lower dose would need to be replenished sooner to maintain the blood levels (maintain a steady state) above the MIC in order to be efficacious. A higher dose would presumably have a drug level/depletion curve that would be above the MIC for a longer period of time, needing less frequent replenishing to achieve the steady state above the MIC.

In the case of clindamycin hydrochloride, the indicated pathogen is *Staphylococcus aureus*. The pioneer sponsor has already established that the level of clindamycin hydrochloride in the blood is at or above the MIC for *Staph. aureus* when an oral dose of 2.5 mg/lb of bodyweight is administered. Indeed, the sponsor of NADA 120-161 states that after the second dose (at 12 hours), the product "adequately maintained a steady state level of clindamycin in dog serum in excess of the minimum inhibitory concentrations." See FOI Summary -- "Corroborative Serum Level Study in Dogs." Based on the sponsor's information establishing that a low dose of clindamycin reaches a steady state quite soon following the initial dose, it is reasonable to expect that a higher daily dose of 5.0 mg/lb, taking longer to deplete by virtue of the fact that there is just more drug available, will reach a steady state above MIC at approximately the same time as two lower doses and be equally as effective. Whether or not the longer depletion (to MIC level) of a single daily dose of 5.0 mg/lb maintains the blood level at or above the MIC in

the same manner as the twice daily dosing of 2.5 mg/lb (pioneer label) is an issue to be determined by a bioequivalence study, and is not a suitability petition issue. Accordingly, no additional evaluation (studies) to establish efficacy is needed.


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Based on the forgoing, Smart Drug respectfully requests that the Commission reverse the decision of CVM and grant its suitability petition.

Respectfully submitted,



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Date

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